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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,588	07/20/2001	David C. Klein	14014.0342U2	3159

23859 7590 10/02/2002

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	6

DATE MAILED: 10/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/910,588	Applicant(s) KLEIN ET AL.	
	Examiner Anne Falk	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 1-20 are pending in the instant application.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). Alterations have been made to the name of Jeffrey A. Kowalak.

Specification

The disclosure is objected to because of the following informalities: The specification refers to "Table 3, experiment 2" on page 19, line 2, but the original text says "Table 2, experiment 2" and the "2" after "Table" is scratched out, with a 3 hand-written over top of the "2." Handwritten corrections are not permitted. An appropriate amendment is required.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* applications of the claimed methods, wherein N-bromoacetyltryptamine is introduced into a cell expressing arylalkylamine N-acetyltransferase (AANAT), does not reasonably provide enablement for any and all *in vitro* applications of the claimed methods, wherein any compound that produces a bisubstrate inhibitor is used to inhibit any acetyltransferase, or any *in vivo* applications of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of producing a bisubstrate inhibitor in a cell, a method of inhibiting the activity of an acetyltransferase in a cell, and a method of inhibiting melatonin production in a cell. The claims read on both *in vivo* and *in vitro* applications of the methods.

The specification fails to provide an enabling disclosure for a method of producing a bisubstrate inhibitor in a cell and a method of inhibiting the activity of an acetyltransferase in a cell, wherein any derivative of an acetyl acceptor substrate is used to inhibit any acetyltransferase because the specification only teaches how to use N-bromoacetyltryptamine to inhibit the activity of AANAT. The specification does not offer any guidance for making and using other substrate derivatives that would be inhibitory to their cognate enzyme. One skilled in the art would not expect that any N-bromoacetylated acetyl acceptor substrate, any N-chloroacetylated acetyl acceptor substrate, or any N-fluoroacetylated acetyl acceptor substrate would be inhibitory for the cognate enzyme. Khalil et al. (June 1998) point out that arylamine N-acetyltransferases are predicted to be resistant to bisubstrate analog inhibitors and that, in fact, this turned out to be the case (p. 6196, column 1, paragraph 1). Undue experimentation would have been required to identify, make, and use appropriate substrate derivatives that produce bisubstrate inibitors that inhibit the activity of any and all acetyltransferases.

The specification fails to provide an enabling disclosure for a method of inhibiting melatonin production in a cell, wherein any derivative of an acetyl acceptor substrate of AANAT is used to inhibit

AANAT because the specification only teaches how to use N-bromoacetyltryptamine to inhibit melatonin production. The specification does not offer any guidance for making and using other substrate derivatives that would inhibit melatonin production in a cell. The working example reveals that rat pinealocytes expressing melatonin can be treated with N-bromoacetyltryptamine to subsequently inhibit the production of melatonin. The effect of other compounds as recited in the claims on melatonin production is unknown.

The specification fails to provide an enabling disclosure for *in vivo* applications of the claimed methods because the *in vivo* effects of the various compounds recited in the claims are unknown. No guidance is offered regarding the *in vivo* effect of introducing an acetyltransferase inhibitor into a cell. The specification does not offer any guidance for the manner of using any of the compounds such as those recited in the claims *in vivo*. The specification does not offer any working examples to demonstrate *in vivo* applications of the claimed methods. The specification teaches that the only use for the *in vivo* applications is to provide therapeutic benefit, to limit adverse effects of certain drugs, or to improve the efficacy of certain drugs. However, the specification does not teach how to use the claimed methods to achieve any of these effects. Furthermore, no guidance is provided with regard to how the compounds would be administered or how often the compounds should be administered to produce the desired therapeutic effect. Moreover, the specificity of the inhibitor is essential for the *in vivo* operability of the claimed methods, yet the specification does not offer any guidance regarding the specificity of the inhibitors to be used in the claimed methods. Further lacking is an assessment of the toxicity of the compounds contemplated for use *in vivo*. In the absence of specific guidance, one skilled in the art would have been required to engage in undue experimentation to practice the claimed methods *in vivo*.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cell comprising a bisubstrate inhibitor comprising N-bromoacetyltryptamine and CoA, does not reasonably provide enablement for any cell comprising any bisubstrate inhibitor of any

acetyltransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for a cell comprising any bisubstrate inhibitor of any acetyltransferase because the specification does not adequately teach how to make and use the full scope of the claimed cells for the reasons discussed above with regard to the claimed methods. The specification only teaches how to make and use a cell comprising the bisubstrate inhibitor comprising N-bromoacetyltryptamine and CoA when AANAT is present in the cell. In the absence of specific guidance, one skilled in the art would not know how to make and use a cell comprising any other bisubstrate inhibitor of either AANAT or another acetyltransferase. The specification teaches that such cells can be used to assay melatonin production or enzyme activity, but the specification does not offer any guidance for identifying other compounds appropriate for the production of cells that could then be used in the manner disclosed. Undue experimentation would have been required for one skilled in the art to make and use the claimed cells.

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of increasing the amount of serotonin in a cell and a method of treating a subject for a disorder caused by a decreased amount of serotonin in a cell.

The specification fails to provide an enabling disclosure for *in vivo* applications of the claimed methods because no guidance is offered regarding the *in vivo* effect of introducing an acetyltransferase inhibitor into a cell. Claim 12 encompasses both *in vitro* and *in vivo* applications of the claimed method. Claims 13 and 14 are directed exclusively to an *in vivo* method. The specification does not offer any guidance for the *in vivo* use of any of the compounds of the types recited in the claims. The specification

does not offer any working examples to demonstrate *in vivo* applications of the claimed methods. Furthermore, no guidance is provided with regard to how the compounds would be administered or how often the compounds should be administered to produce the desired therapeutic effect or to increase the amount of serotonin in a cell. Moreover, the specificity of the inhibitor is essential for the *in vivo* operability of the claimed methods, yet the specification does not offer any guidance regarding the specificity of the inhibitors to be used in the claimed methods. Further lacking is an assessment of the toxicity of the compounds contemplated for use *in vivo*.

The specification fails to provide an enabling disclosure for the method of increasing the amount of serotonin in a cell. The claim (Claim 12) encompasses both *in vitro* and *in vivo* applications of the method. However, the specification is not enabling for either one because it lacks adequate guidance for increasing the amount of serotonin in a cell using the method disclosed. Although a working example demonstrated the inhibition of melatonin production in cells in culture when the cells were treated with N-bromoacetyltryptamine, the amount of serotonin present in the cells was not measured.

Given the limited guidance in the specification, the lack of *in vivo* working examples, and the unpredictability in the art regarding the physiological effects of compounds such as those recited in the claims, undue experimentation would have been required for one skilled in the art to practice the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite in its recitation of "[t]he method of claim 15" because Claim 15 is directed to a cell not a method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-8, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khalil et al. (June 1998).

The claims are directed to a method of producing a bisubstrate inhibitor in a cell, wherein an alkylating derivative of an acetyl acceptor substrate for an acetyltransferase present in the cell is introduced into the cell.

Khalil et al. (June 1998) disclose a potent and specific inhibitor of arylalkylamine N-acetyltransferase (AANAT). The inhibitor, compound 1, is a synthetic bisubstrate analog. The authors contemplate that inhibitors of melatonin biosynthesis could have therapeutic roles in mood and sleep disorders and that the key enzyme to be targeted in this regard is serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, AANAT).

Since specific AANAT inhibitors may have therapeutic value, one skilled in the art would have been motivated to introduce the inhibitor into a cell expressing the enzyme in order to determine the effect of the inhibitor on the activity of the enzyme in cells in culture and to assess the cytotoxicity of the compound. A reasonable expectation of success would have been anticipated because the bisubstrate analog would be expected to readily diffuse across the cell membrane and exert its inhibitory effect intracellularly. Therefore, it would have been obvious to one skilled in the art to have introduced a known inhibitory compound into cells in culture to determine its effect on enzyme activity in a biological

context, thereby producing cells comprising a bisubstrate inhibitor. One skilled in the art would have recognized the advantage of using an exogenous nucleic acid encoding the appropriate acetyltransferase to generate a recombinant cell line that could be used to assay the intracellular inhibitory effect of the compound described by Khalil et al. as well as other candidate compounds.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1-3, 6-8, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khalil et al. (November 1998).

The claims are directed to a method of producing a bisubstrate inhibitor in a cell, wherein an alkylating derivative of an acetyl acceptor substrate for an acetyltransferase present in the cell is introduced into the cell.

Khalil et al. (November 1998) disclose the arylalkylamine N-acetyltransferase (AANAT) inhibitor α-trifluoromethyltryptamine. The inhibitor served as a modest competitive inhibitor (Abstract). The authors contemplate that "[i]n principle, a detailed understanding of the substrate selectivity and catalytic mechanism of AANAT could lead to the development of specific AANAT inhibitors that might have therapeutic value in sleep and mood disorders" (p. 30321, column 2, paragraph 1). The study looks at the effects of various AANAT substrate derivatives on enzyme activity.

Since specific AANAT inhibitors may have therapeutic value, one skilled in the art would have been motivated to introduce the inhibitor into a cell expressing the enzyme in order to determine the effect of the inhibitor on the activity of the enzyme in cells in culture and to assess the cytotoxicity of the compound. A reasonable expectation of success would have been anticipated because a small molecule such as α-trifluoromethyltryptamine would be expected to readily diffuse across the cell membrane and exert its inhibitory effect intracellularly. Therefore, it would have been obvious to one skilled in the art to have introduced a known inhibitory compound into cells in culture to determine its effect on enzyme

activity in a biological context, thereby producing cells comprising the inhibitor. One skilled in the art would have recognized the advantage of using an exogenous nucleic acid encoding the appropriate acetyltransferase to generate a recombinant cell line that could be used to assay the intracellular inhibitory effect of the compound described by Khalil et al. as well as other candidate compounds.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER